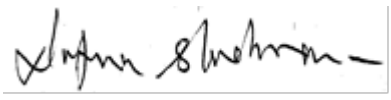
To our Stakeholders,

As we are all aware, COVID-19 has presented significant challenges not only in Canada but globally, and over the past months, the focus has been to prevent the spread and contain this virus, and keep people safe and healthy. Vaccines offer us light at the end of the tunnel, but we know there are many challenges with the delays in shipment, etc. and with the increased transmission of new variants, the situation is only getting worse before it gets any better.

At the University Health Network (UHN) which is the lead site of the IPART Research Program in Toronto, research operations have been halted since mid-March 2020, as well as in all other core and collaborating sites of IPART across Canada and internationally. All coordinating efforts are in place at UHN to ensure that our processes are aligned and in compliance with municipal and provincial directives, and certainly in all other sites as well. Towards the last quarter of 2020, we have transitioned to a gradual restart phase on research activities; however, with the fast resurgence of COVID cases in 2021, new restrictions are in place which limit onsite access for patients and staff alike, and limiting density for research laboratories. This approach has allowed for a safe and productive work environment which is also aligned with those at other research hospitals.

Therefore, while recruitment across the IPART network is gradually improving, sample dispatch to our biobank facility at UHN from core and collaborating sites remains suspended. These sites continue to keep their samples in their respective sites until further notice. In light of this reality, our productivity in IPART has somehow been affected although each site of IPART continue conducting research activities the best possible way allowable under the present circumstances, but not to its fullest capacity. We are therefore providing you our progress report as outlined below, with the resources available to us at this time. Please bear with us during these unprecedented times amid COVID-19.

Thank you for your understanding and cooperation. Stay safe!!!!



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PROGRESS REPORT

DATABASE AND BIOBANKING UPDATE

DATABASE

IPART has the largest collection of well characterized patients with PsD (psoriatic diseases) followed longitudinally in the world. It has successfully established a large multicenter cohort of well phenotyped patients with psoriasis without psoriatic arthritis (PsC) and psoriatic arthritis (PsA), tracked on a web-based database which includes clinical, laboratory, and imaging information, linked to biologic specimens.

As of January 31, 2021												
	TWH	WCH	St. John's	Vancouver	Ann Arbor	Rochester	London	Winnipeg	Israel	Halifax	Argentina	Ottawa
PSA	1631	226	608	95	15	238	179	44	213	4	4	17
Psoriasis	705	377	81	44	68	216	5	181	26	21	9	0
Total	2336	603	689	139	83	454	184	225	239	25	13	17
Female*	44.4	56.1	52.8	50.4	48.2	55.4	40.8	50.2	56.9	36.0	92.3	58.8
Caucasian*	85.5	74.7	99.2	64.0	98.8	89.7	94.6	82.7	79.5	92.0	75.0	94.1
Visits PS	4.0	2.0	1.1	1.9	2.6	2.1	1.8	3.6	1.2	1.5	1.0	N/A
Visits PSA	13.4	4.8	1.4	1.9	2.0	3.0	4.2	4.0	3.3	1.3	1.0	1.0
Age Ps	30.1	31.9	29.7	31.2	30.2	32.2	33.1	31.2	36.2	28.4	31.1	35.7
Age PsA	38.2	42.9	39.5	37.5	41.5	40.5	42.7	41.5	46.0	46.0	40.3	44.6
DD Ps	19.5	16.6	17.8	23.0	13.3	20.0	18.6	23.3	16.1	23.0	17.8	N/A
DD PsA	16.4	6.9	10.7	14.1	11.4	12.3	13.0	12.7	11.3	2.5	10.5	13.3
*=%, Ps = Psoriasis; PsA = Psoriatic arthritis; DD = disease duration at presentation												

In summary:

	PsA	PsC	**TOTAL**
Number of patients	3276	1733	**5007**

Establishing a common clinical database has been a significant achievement for the IPART network and checks off a major goal from the original proposal. The database has been a foundational asset we developed from which all projects and activities have stemmed. It is the database which has allowed us to address our objectives; 1) identify susceptibility factors for PsA among patients with PsC and 2) to identify risk factors for disease severity among patients with PsC and PsA.

New functionality has been added to DADOS to import lab results from external sources (Lifelabs) and internal databases. This is has streamlined the process of adding data to the database and improved quality.

IPART TORONTO BIOBANK

The IPART biobank continues to grow and expand as our research endeavors progress. We have built a biobank that contains the world's largest collection of biosamples that is matched with detailed clinical phenotype and molecular data for PsA and PsC cohorts.

The core laboratory is based at Toronto Western Hospital and receives the majority of IPART biosample collection with several of the core collaborating sites also maintaining local biobanks for IPART. Vancouver, Rochester, Ann Arbor and St. John's all maintain biorepositories for IPART. The core IPART

laboratory is accredited for biosafety standards and continues to maintain high standards for consistent sample processing and handling, with standard operating procedures and quality control. We have also adopted ethical guidelines; have privacy protocols and a governance structure which ensures our biobank is operating within industry standards.

With substantial biobanking as part of our program, we are now able to better manage the large number of samples with full auditing and tracking capabilities. Every single aliquot will be monitored and tracked for collection, storage, allocation and use. The system even sends alerts for when more samples are required to replenish depleting stocks which is very useful in the use of our DNA biobank. This is one of the ways in which we have improved our biobanking practice.

The implementation of biobank sample management software, **CaTissue,** is almost complete with the final upload due very soon. The system has been linked to our clinical database which enables us to search data sources from biological samples available and matching clinical data.

Here is the latest update of biosamples stored in our facility:

	TWH PsA	TWH PsC	Women's College	St. John's	London	Halifax	Winnipeg
DNA	1346	659	511	168	168	26	223
Serum	9351	1855	724	490	363	35	264
RNA	8026	762	798	41	393	35	169
Synovial Fluid	177		23				

RESEARCH UPDATE (2020-2021)

In the past years, IPART has made significant progress in its research program, particularly in the areas of clinical, genetic, and biomarker studies. The following projects are on-going:

A Progress Report by Dr. James T. Elder
IPART Core Site - University of Michigan, USA

Recent Genetic Studies:

Expanded Meta-GWAS of Psoriasis: We published a meta-analysis of PsV that incorporated patient-reported psoriasis data from 23andMe (1) along with data from 7 other Caucasian cohorts, with a combined effective sample size (N_{eff}) >39,000 individuals. That study identified 16 psoriasis susceptibility loci newly achieving GW significance, increasing the number of psoriasis loci to 63 and explaining ~28% of heritability. Functional analysis highlighted the roles of IFN signaling and the NFκB cascade, and showed that psoriasis signals are enriched in T-cell regulatory elements (CD8 and CD4 T-cells including Th0, Th1 and Th17). In addition, our most recent meta-analysis of PsA vs. controls in 27,360 individuals (11,024 PsV, 3,674 PsA, 3,566 PsC, and 16,336 controls) identified 13 GW significant non-MHC signals (2), three of which *(NFKBIZ, IL13, PRDX5)* newly reached GW significance.

PsA Prediction: We recently developed a computational pipeline to identify and use independent genetic signals for distinguishing PsV vs. normal controls, and PsA vs. PsC , with the objective of generating an innovative way to predict those ~25% of incident PsV cases that are at risk for PsA. In the largest PsA/PsC study to-date, consisting of 6 cohorts with >7,000 genotyped PsA and PsC patients, we increased the numbers of PsA and PsC samples with GWAS coverage we identified 9 new loci for psoriasis or its subtypes, and observed that active enhancers in lymphocytes are highly enriched among subtype-specific loci. We achieved 0.82 area under the receiver operator curve (AUROC) in distinguishing PsA vs. PsC, and >90% precision for PsA prediction among psoriatic patients with the greatest genetic load.

Integrative Studies of PsA vs. PsC:. In a 2019 paper (3), we asked whether appropriate epigenomic elements (H3K27ac marks for active enhancers) could reveal information about associated loci with significance shy of the GW threshold. We overlapped 165 suggestively significant ($p < 1 \times 10^{-4}$) PsA vs. PsC markers from 49 distinct loci outside the MHC against H3K27ac chromatin marks extracted from public databases , yielding 53 markers (18 loci) overlapping active enhancers for any cell type. Notably, we found significant enrichment of PsA vs. PsC signals only in osteoblasts and chondrogenic differentiated cells. Significantly, six of the ten suggestive loci overlapping H3K27Ac peaks encompass genes differentially expressed (FDR < 5%) in differentiated osteoblasts, including genes participating in Wnt signaling such as *RUNX1*, *FUT8*, and *CTNNAL1*.

EPIGENOMIC STUDIES

eQTL Studies of Disease-relevant Immunocytes*:* With the support of R01 AR042742, we utilized the U-M Flow Cytometry Core to generate 9 cell fractions from PBMC: mDC, four fractions of unstimulated CD3+CD45RO+ memory T cells (CD4+CLA-, CD4+CLA+, CD8+CLA-, CD8+CLA+) and the same 4 fractions after 24 hours of stimulation of the CD1c- column flow-through (primarily T-cells) with anti-CD3/anti-CD28 beads. We have completed flow-sorting, RNA-seq library formation and sequencing, high-density genotyping using Illumina Infinium Omni5Exome-4 arrays that contain ~4.6 million whole-genome and functional exonic variants, followed by imputation using the TOPMed reference panel (4), generating an unprecedented collection of 156 individuals (88 psoriasis cases and 68 healthy controls) for genetic analysis of gene expression, yielding 1,138 RNA-seq libraries passing QC (MQ30, 25M reads/sample). RNA-seq libraries were prepared and sequenced by the U-M Advanced Genomics Core. Our target cell count for each type of library was 50,000 cells.

In a 2021 SID abstract (5), we reported data from 126 subjects, totaling 955 libraries passing QC. Principal components analysis (PCA) of RNA-seq reads revealed clear separations on the basis of activation, CD4/CD8, gender, and skin homing, with lesser discrimination between psoriatic and healthy individuals. We further revealed 139 DEGs when comparing the CD4/CD8 T-cells in psoriatics vs. controls, which were most significantly enriched for “IL-17 signaling pathway” (KEGG, adj. p=0.0086). Notably, IL-17 pathway genes such as *IL17A*, *IL22*, and *CCL20* were more strongly induced by CD3/CD28 in CLA+ vs. CLA- T-cells (2-4-fold). 132 psoriasis DEGs were found in CD3/CD28-stimulated CD4 T-cells vs. only 27 in resting CD4 T-cells (63 and 39, respectively, for CD8). In mDC, 276 psoriasis DEGs were most significantly enriched for “cytokine-cytokine receptor interaction” (KEGG, adj. $p=4.14 \times 10^{-5}$). These results identify psoriasis-related, T-cell activation-enhanced DEGs in blood-derived immunocytes, highlighting a subtle but important systemic component of psoriatic immune-mediated inflammation.

In a 2020 SID abstract (6), we reported an analysis of paired RNA-seq and ATAC-seq data on T-cells involving a subset of 47 individuals, identifying DEGs (FDR<0.05, |log2 (FC)|>0.585) as functions of CD4/CD8, CLA+/-, and 0 vs. 24h CD3/CD28 activation. Across the resulting 8 comparisons, we found from 97 to 2384 DEGs as a function of skin-homing, and from 5817 to 7502 DEGs as a function of activation. KEGG analysis of skin-homing DEGs revealed enrichment for "osteoclast differentiation" ($p=4.3x10^{-11}$) and "Th17 differentiation" ($p=2.4x10^{-5}$) in unstimulated CLA+ vs. CLA- CD4 T-cells. Even stronger enrichment for "Th17 differentiation" was observed after CD3/CD28 stimulation ($5.8x10^{-10}$), with *IL17A, IL17F, IL23R,* and *IL22* appearing as DEGs only after activation. Unstimulated CD8 T-cells manifested similar enrichments as a function of skin homing ($p=3.0x10^{-8}$ and $4.2x10^{-4}$, respectively).

Chromatin-QTL (chrQTL) Studies: Using the same cell fractions described above, ATAC-seq libraries were prepared in our laboratory following established protocols , and sequenced by the Advanced Genomics Core. Library construction and sequencing of up to nine ATAC-seq libraries per individual passing QC is now complete for the same 156 individuals, yielding 1,195 libraries after QC. PCA revealed strong separation of mDC vs. T-cells, resting vs. activated T-cells, and CD4 vs. CD8 T-cells. At the 2019 Montagna Symposium (7), we presented data from a subset of these individuals, revealing 36,716 differentially accessible regions (DARs) in CLA+CD4 T-cells and 24,932 DARs in CLA- CD4 T cells as a function of stimulation (FDR<0.05, |log2(FC)| > 1). For CD8+ T cells, corresponding DARs numbered 35,296 and 28,594, respectively. Fewer DARs were identified comparing CLA+ vs. CLA- T cells (8,301 and 2,818 DARs for CD4 and CD8, respectively). Transcription factor (TF) footprinting using CENTIPEDE (75) revealed highly significant enrichment for AP1-family TF footprints in CD3/CD28-activation-associated DARs for skin-homing CD4 T-cells. These results are in good overall agreement with the RNA-seq results, indicating that T-cell activation leads to chromatin alterations related to AP1-family TF activation, and suggesting a nexus between skin-homing and cytokine-mediated Th17 differentiation.

BIOMARKER STUDIES

Genetic and Genomic Biomarkers: On the genomic biomarker front, we have conducted mRNA and micro-RNA (mi-RNA) transcriptome experiments utilizing blood samples stored at study entry, which were paired with additional blood samples from incident PsA cases at the onset of PsA development. We analyzed 65 pairs of converters from PsC to PsA at 3 centers (U-M, UHN, and Rochester, 19, 36, and 10 pairs, respectively). The time from initial PsC ascertainment to PsA conversion varied from 112 to 3,187 days (median 1,087 days). We analyzed 311 miRNAs with a mean abundance of ≥1 read per sample. These analyses yielded 60 miRNAs and 1,516 mRNAs meeting the DE criteria of FDR < 10% and |log2FC| ≥ log2(1.5). Using miRDB (79) to relate miRNAs and their mRNA targets that were expressed in our datasets, we identified 28,829 relationships involving 282 miRNAs targeting 4,525 genes. 54 of these miRNAs were DE (27 up and 27 down in PsA), and they targeted 1,580 mRNAs, 55 of which were also DE (44 up, 11 down, avg ~4-fold). Among the 23 mRNA targets of "up" miRNAs, 16 mRNAs were increased and 7 were decreased (avg ~2-fold) in PsA samples. Among the 35 targets of "down" miRNAs, 31 target mRNAs were increased and 4 were decreased (avg ~8-fold). Most of the 55 DE mRNAs were targeted by only one DE miRNA, with the other mRNAs ranging from 2 to 8 miRNAs. For the mRNAs targeted by only one miRNA, there was a strong correlation between the expression of DE miRNAs and their DE mRNA targets, as assessed by linear modeling.

Metabolomic Biomarkers: We performed a metabolomic analysis of PsC-to-PsA converters on the Metabolon platform, involving 50 pairs of serum samples from PsC-to-PsA converters from Michigan, Toronto, and Rochester (31, 10, and 9 pairs, respectively). Median time to conversion was 1,087 days (range 112 - 3,187). Metabolomic profiling of these samples revealed multiple biochemical signatures related to the pathophysiology of the disease. Following log transformation and imputation of missing values with the minimum observed value, 293 out of 1,299 biochemicals were significantly ($p<0.05$ by matched pairs t-test) altered in PsA vs. PsC (275 up in PsA, 18 down), with another 110 altered at $0.05<p<0.1$ (104 up, 6 down). For example, numerous metabolic indications of increased inflammation were observed in the affected cohort with significant elevations in inflammatory lipid mediators, free fatty acids, endocannabinoids, and sphingolipids. Converters also exhibited evidence of perturbed energetics, both from lipid oxidation, as well as a switch to Warburg metabolism with a dependence on glutaminolysis. Elevated oxidative stress was accompanied by an altered antioxidant status (notably increased taurine, suggestive of a protective role against neutrophil- and macrophage [MΦ]-derived oxidants) (80). The metabolism results are collectively consistent with the broader T-cell pathobiology of psoriasis since a large body of evidence shows that T-cells switch from oxidative phosphorylation to less efficient aerobic glycolysis when activated (Warburg metabolism) . Random forest analysis was used to identify metabolites that differentiated between PsC and PsA groups, resulting in a predictive accuracy of 74% (compared to 50% by random chance), demonstrating that individual metabolites were able to classify the two groups with a good degree of confidence. The metabolites with greatest effects on classification were largely lipids, including polyunsaturated fatty acids, lysoplasmalogens, lysophospholipids, and metabolites associated with glutamate metabolism (e.g. gamma-glutamylglutamate).

PUBLICATIONS

1. Tsoi LC, Stuart PE, Tian C, Gudjonsson JE, Das S, Zawistowski M, et al. Large scale meta-analysis characterizes genetic architecture for common psoriasis associated variants. Nat Commun. 2017;8:1538.
2. Patrick MT, Stuart PE, Raja K, Gudjonsson JE, Tejasvi T, Yang J, et al. Genetic signature to provide robust risk assessment of psoriatic arthritis development in psoriasis patients. Nat Commun. 2018;9(1):4178.
3. Patrick MT, Stuart PE, Raja K, Chi S, He Z, Voorhees JJ, et al. Integrative Approach to Reveal Cell Type Specificity and Gene Candidates for Psoriatic Arthritis Outside the MHC. Front Genet. 2019;10:304.
4. Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature. 2021;590(7845):290-9.
5. Zhang Z, Zhao Y, Tsoi LC, Nair RP, Stuart PE, Wen X, et al. Differential gene expression in psoriatic vs. normal T-cells is enhanced by CD3-CD28 activation [abstract]. J Invest Dermatol. 2021.
6. Zhang X, Tsoi LC, Nair RP, Stuart PE, Wen X, Elder JT. Differential gene expression and chromatin accessibility reveals Th17 polarization in skin-homing T cells [abstract]. J Invest Dermatol. 2020.Zhang Z, Tsoi LC, Nair RP, Stuart PE, Pique-Regi R, Wen R, et al. Differential accessibility of AP1-family binding sites in CD3-CD28-activated vs. resting T-cells [abstract]. J Invest Dermatol. 2019.

A Progress Report by Dr. Christopher Ritchlin
IPART Core Site - University of Rochester, USA

The IPART Registry is a longitudinal cohort of psoriasis (Ps) and psoriatic arthritis (PsA) patients. The primary goal of this registry is to understand the genetic, molecular, cellular and environmental variables that underlie the transition from psoriasis to PsA, which takes place in approximately 30% of psoriasis patients who develop arthritis. We have several projects with dovetail with this database and we are preparing manuscripts which address different factors linked to this transition. We are also downloading out key demographic and phenotypic data from the IPART data base to our Biologic Lab Information Server (BLIS) at the University to link these data to the location and analysis of linked biosamples.

The Rochester site has recruited approximately 500 patients since the registry started. We are routinely the second or third most active site out of 8 other centers. We anticipate that over the next year, based on previous experience, we will recruit 100 patients per year who will be followed longitudinally.

Projects Linked to IPART

- R01 DC-STAMP
- National Psoriasis Foundation Biomarker Grant
- National Psoriasis Foundation Discovery Grant
- National Psoriasis Foundation Prevention of Psoriasis (PPI) Initiative

Grant Proposals Submitted that use IPART Registry for Patient Recruitment

- "The Fractalkine-CX3CR1 Axis in Psoriatic Arthritis-Mechanisms and Biomarker Potential" R21 submission June 2021
- Accelerating Medicine Partnership Program 2.0. RFA anticipated early 2021 and we will be submitting a proposal in collaboration with Dr. Jose Scher and Dr. Wilson Lia (UCSF Dermatology). The registry will be a key resource for recruiting patients for this effort. Letter of intent released March 2021 and RFA to be published soon.

DISCOVERIES

- 44 Ps patients followed for 4 years and 10 developed PsA. Variables associated with development of PsA included baseline ultrasound imaging abnormalities ($p<.001$) and osteoclast precursor populations ($p<.01$). (Manuscript submitted)
- We are following patients who are treated with methotrexate or anti-TNF agents and measuring serial Dendritic Cell- Specific Transmembrane Protein (DC-STAMP)-CD14+ expression by flow cytometry in these subjects to determine if DC-STAMP level decrease from baseline to 2 weeks predicts response at 16 weeks. The current RO-1- funded study is still recruiting patients but recruitment was delayed due to the pandemic. We have completed recruitment and we are analyzing the data with anticipated manuscript submission June 2021.
- In the Discovery grant, we found upregulated RANKL mRNA in the skin biopsies of patients with PsA compared to Ps. (Manuscript submitted).
- In the biomarker proposal, we identified several coding and non-coding mRNAs that were associated with PsA more strongly than Ps. We performed RT-PCR to confirm these candidates. We also sent 120 samples from the IPART database to Metabolon from patients with Ps, PsA and those who

transitioned from Ps to PsA for metabolomics analysis. We have identified metabolomic signatures that mark transition from Ps to PsA in subjects in the IPART database in Rochester. (Manuscript to be submitted April 2021)

- We collect DNA samples from all of our patients that are sent to JT Elder at University of Michigan and we included in the dataset in the Stuart paper listed below. This paper identified IL-23R and TNFAIP3 as genetic risk factors in PsA.
- Relevant publications with patients from IPART database.

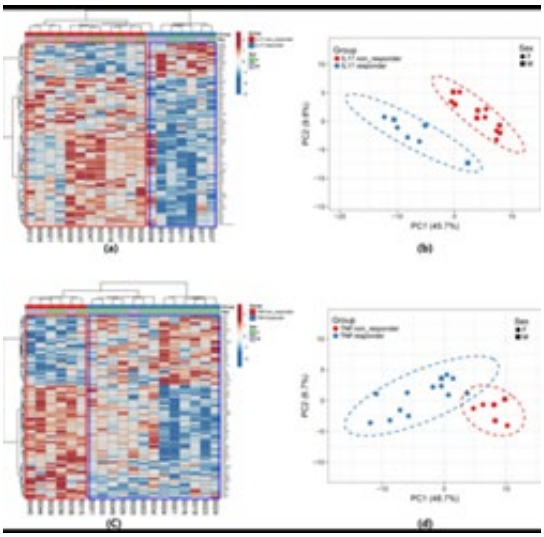
PUBLICATIONS

1. Chiu YH, Mensah KA, Schwarz EM, Ju Y, Takahata M, Feng C, McMahon LA, Hicks DG, Panepento B, Keng PC, Ritchlin CT. Regulation of human osteoclast development by dendritic cell-specific transmembrane protein (DC-STAMP). J Bone Miner Res. 2012 Jan;27(1):79-92. PMCID: PMC3304467
2. Chiu YG, Ritchlin CT. Characterization of DC-STAMP+ Cells in Human Bone Marrow. J Bone Marrow Res. 2013 Jul 19;1. pii: 1000127. PMCID: PMC4238037
3. Rosenberg A, Fan H, Chiu YG, Bolce R, Tabechian D, Barrett R, Moorehead S, Baribaud F, Liu H, Peffer N, Shealy D, Schwarz EM, Ritchlin CT. Divergent gene activation in peripheral blood and tissues of patients with rheumatoid arthritis, psoriatic arthritis and psoriasis following infliximab therapy. PLoS One. 2014 Oct 21;9(10):e110657. doi: 10.1371/journal.pone.0110657. PMCID: PMC4204991
4. Stuart PE, Nair RP, Tsoi LC, Tejasvi T, Das S, Kang HM, Ellinghaus E, Chandran V, Callis-Duffin K, Ike R, Li Y, Wen X, Enerbäck C, Gudjonsson JE, Kõks S, Kingo K, Esko T, Mrowietz U, Reis A, Wichmann HE, Gieger C, Hoffmann P, Nöthen MM, Winkelmann J, Kunz M, Moreta EG, Mease PJ, Ritchlin CT, Bowcock AM, Krueger GG, Lim HW, Weidinger S, Weichenthal M, Voorhees JJ, Rahman P, Gregersen PK, Franke A, Gladman DD, Abecasis GR, Elder JT. enome-wide Association Analysis of Psoriatic Arthritis and Cutaneous Psoriasis Reveals Differences in Their Genetic Architecture. Am J Hum Genet 2015 Dec 3;97(6):816-36.
5. Eder L, Harvey P, Chandran V, Rosen CF, Dutz J, Elder JT, Rahman P, Ritchlin CT, Rohekar S, Hayday R, Barac S, Feld J, Zisman D, Gladman DD. Gaps in Diagnosis and Treatment of Cardiovascular Risk Factors in Patients with Psoriatic Disease: An International Multicenter Study. J Rheumatol. 2018 Mar;45(3):378-384. doi: 10.3899/jrheum.170379. Epub 2018 Feb 1.
6. Scher J., Ogdie A, Merola J, Ritchlin CT. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nature Rev Rheum. 2019; 15:153.
7. Eder L, Lee K, Chandran V, Widdifield J, Drucker A, Ritchlin C, Rosen C, Cook R, Gladman D. The Prediction of Psoriatic Arthritis Tool (PRESTO) Study – Interim Report [abstract]. *Arthritis Rheumatol.* 2020; 72 (suppl 10). https://acrabstracts.org/abstract/the-prediction-of-psoriatic-arthritis-tool-presto-study-interim-report/.
8. Thiele RG, Chiu YG, Huertas N, Li D, Feng C, Moorehead S, Bell C, Ritchlin CT. Serum, Cellular and Imaging Markers of Arthritis in Psoriasis Patients and Healthy Controls [abstract]. *Arthritis Rheumatol.* 2018; 70 (suppl 10). https://acrabstracts.org/abstract/serum-cellular-and-imaging-markers-of-arthritis-in-psoriasis-patients-and-healthy-controls/.

The following projects are on-going at the genetic core site in Newfoundland:

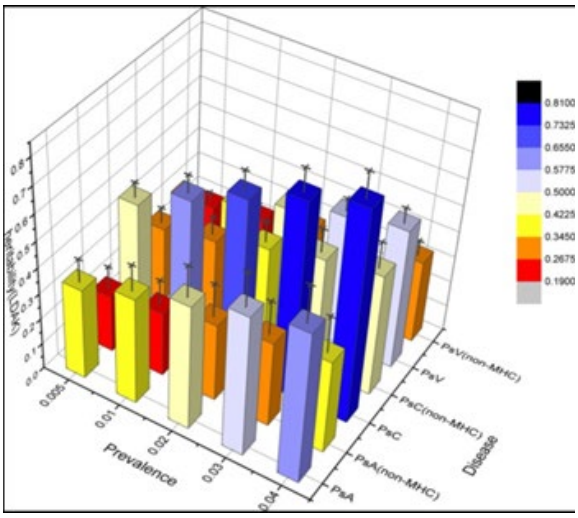
Rho-GTPase Pathways may differentiate treatment response to TNF-alpha and IL-17A inhibitors in psoriatic arthritis.

There is a pressing need to develop a coherent strategy for effective initial and subsequent selection of biologic agents. We interrogated 40 PsA patients initiating either tumour necrosis factor inhibitors (TNFi) or interleukin-17A inhibitors (17Ai) for active PsA. Patients achieving low disease activity according to the Disease Activity Index for PsA (DAPSA) at 3 months were classified as responders. Baseline and 3-month $CD4^+$ transcript profiling were performed, and novel signaling pathways were identified using a multi-omics profiling and integrative computational analysis approach. Using transcriptomic data at initiation of therapy, we identified over 100 differentially expressed genes (DEGs) that differentiated IL-17Ai response from non-response and TNFi response from non-response. Integration of cell-type-specific DEGs with protein-protein interactions and further comprehensive pathway enrichment analysis revealed several pathways. Rho GTPase signaling pathway exhibited a strong signal specific to IL-17Ai response and the genes, RAC1 and ROCKs, are supported by results from prior research. Our detailed network and pathway analyses have identified the rewiring of Rho GTPase pathways as potential markers of response to IL17Ai but not TNFi. These results need further verification.



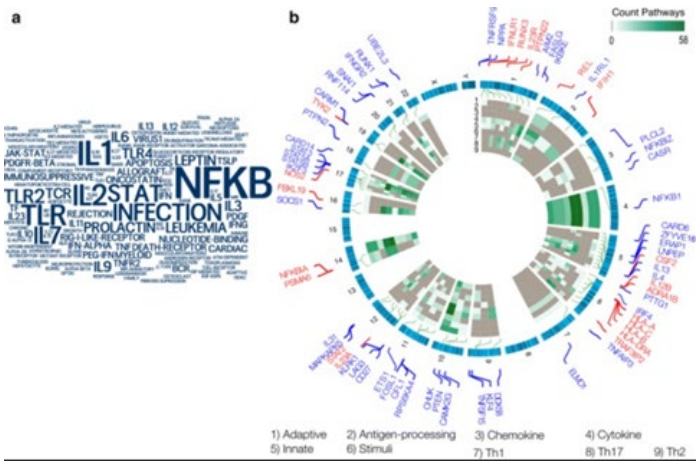
Quantifying Differences in Heritability among Psoriatic Arthritis (PsA), Cutaneous Psoriasis (PsC) and Psoriasis vulgaris (PsV)

Chronic plaque psoriasis and psoriatic arthritis are multifactorial inter-related diseases with strong genetic contributions. Better elucidation of the heritability of psoriatic disease subsets is important for identifying novel genes, risk stratification and potential clinical applications. In this study, we used two mixed-effect modelling methodologies to assess the additive contribution of common single nucleotide polymorphisms from genome-wide association studies to estimate the heritability of cutaneous psoriasis, psoriasis vulgaris and psoriatic arthritis. We found that cutaneous psoriasis and psoriatic arthritis both exhibit considerable heritability, with a greater contribution coming from cutaneous psoriasis.



Complexities in Genetics of Psoriatic Arthritis

Focusing on functional pathways that connect previously identified genetic variants can increase our understanding of psoriatic diseases. The genetic architecture differs between psoriatic arthritis and cutaneous-only psoriasis with arthritis-specific signals in linkage disequilibrium independent of the published psoriasis signals. Integrative medicine is helpful in understanding cellular mechanisms of psoriatic diseases. Careful selection of the psoriatic disease cohort has translated into mechanistic differences among psoriatic arthritis and cutaneous psoriasis.



PUBLICATIONS

Listed below are the publications related to the above projects:

1. Rahmati S, O'Rielly DD, Li Q, Codner D, Dohey A, Jenkins K, Jurisica I, Gladman DD, Chandran V, Rahman P. Rho-GTPase pathways may differentiate treatment response to TNF-alpha and IL-17A inhibitors in psoriatic arthritis. Sci Rep. 2020 Dec 10;10(1):21703. doi: 10.1038/s41598-020-78866-2.
2. Li Q, Chandran V, Tsoi L, O'Rielly D, Nair RP, Gladman D, Elder JT, Rahman P. Quantifying Differences in Heritability among Psoriatic Arthritis (PsA), Cutaneous Psoriasis (PsC) and Psoriasis vulgaris (PsV). Sci Rep. 2020 Mar 18;10(1):4925.
3. Rahmati S, Tsoi L, O'Rielly D, Chandran V, Rahman P. Complexities in Genetics of Psoriatic Arthritis. Curr Rheumatol Rep. 2020 Mar 12;22(4):10. doi: 10.1007/s11926-020-0886-x.

A Progress Report by Dr. Jan Dutz

IPART Core Site – University of British Columbia, Vancouver, Canada

The following clinical studies are ongoing in the Vancouver core site:

Combination tsDMARDs

We have collected a case series of patients with severe psoriatic arthritis who have not had adequate response in all domains of their disease despite multiple trials of biologics. In our case series of 5 patients, we have noted good success combining tofacitinib 5mg twice daily with biologics that work on the IL 17/23 axis (ustekinumab, secukinumab, ixekizumab, guselkumab, and risankizumab). These patients were followed from 3-14 months with no serious adverse events to date. Future studies will be needed to confirm whether combining tofacitinib with these biologics indeed has a synergistic effect and whether there is an increased risk of adverse events. This case series was presented at CRA in 2021 and has been submitted for publication.

Switching Between IL17 Inhibitors

We have collected a case series of 8 patients who have psoriatic arthritis and active inflammatory arthritis despite secukinumab 300mg monthly. We switched these patients to ixekizumab 80mg every 4 weeks. Most patients had noticed some improvement in tender and swollen joint counts although only 3/8 had complete resolution of swollen joints. Two patients did not notice any benefit with the switch. Only 4 and 2 patients had dactylitis and enthesitis on secukinumab respectively and all had complete resolution after the switch. This suggests that patients with active psoriatic arthritis despite secukinumab may still derive benefit by switching to ixekizumab. Larger studies will be needed to confirm this finding. This case series was presented at CRA in 2021 and has been submitted for publication.

PUBLICATIONS/PRESENTATIONS

Listed below were the posters presented during the CRA annual scientific meeting 2021 related to the above projects, and publications were submitted:

1. Combination Therapy with Tofacitinib and IL-23 Inhibition for the Treatment of Refractory Psoriatic Arthritis. Poster presentation CRA 2021
2. A Retrospective Study on the Effectiveness of Ixekizumab after treatment with Secukinumab for patients with active Psoriatic Arthritis. Poster presentation CRA 2021

Progress Report by Drs. Dafna Gladman, Vinod Chandran and Cheryl Rosen
IPART Toronto Core Site – UHN – Toronto Western Hospital, Canada

Despite measure difficulties due to the COVID19 pandemic, we have continued our work. The PsA clinic at UHN has been restricted in the number of patients who can attend in person, but we have continued to provide clinical care virtually, bringing patients into the clinic when therapeutic decisions need to be made. However, we have been hampered in our ability to carry out our laboratory work. The laboratory was closed for the first several months of the pandemic, and when it re-opened in June, we were restricted to half the staff working at any one time. Moreover, the fact that patients were not coming into the clinic prevented us from getting samples necessary for our research. Most of the work we have done during the pandemic was based on samples already stored in the biobank. We have a number of ongoing studies which involves the IPART bio samples.

We were able to publish several papers based on work done prior to the pandemic which are presented here starting with the clinical studies then the translational studies.

CLINICAL STUDIES

- Using the IPART standard protocol which includes data on physician assessment and patient reported outcome necessary to calculate the PsA disease activity score (PASDAS) and the disease activity of PsA (DAPSA) and patients' acceptable symptom state (PASS) collected during clinic visits, we identified PASS thresholds for the PASDAS (3.79) and DAPSA (11.1) with high specificity and sensitivity. Lower disease activity scores and older age were associated with PASS (1).

- We compared patients with PsA to patients with ankylosing spondylitis with and without psoriasis. The study demonstrated that axial PsA seems different from ankylosing spondylitis with or without

psoriasis in terms of demographic features, genetic factors, clinical and radiographic features. We thus demonstrated that axial PsA seems to be a distinct entity (2).

- Using PsA patients followed at the Toronto Western Hospital IPART cohort, we determined the cut-off value of PASDAS that defines the minimal disease activity (MDA) state. In our cohort a PASDAS score of <3.2 reflects MDA (4). We also validated the PASDAS using a shorter form of the Medical Outcome Study Short-Form 12 (SF-12). This modified PASDAS highly correlates with the original PASDAS which uses the SF-36, and has very low misclassification rate, suggesting that it can replace the original PASDAS (5).

- We have updated our mortality studies to reflect the current therapeutic landscape. Our previous studies demonstrated an increased mortality risk in PsA. Those studies were performed prior to wide spread use of biologic therapy. The current study which extends the cohort into the biologics era demonstrated no increased mortality risk among patients with PsA, suggesting that better control of the disease provides a survival advantage to our patients (6).

- Patients with PsA suffer from a number of comorbidities. We have now added the fact that liver disease is common among patients with PsA, with a prevalence of 32%. Liver abnormalities, which included drug induced hepatitis and fatty liver disease most commonly, were associated with high body mass index, daily alcohol intake, and a higher burden of disease (7).

- A study assessing the relationship between clinical examination and sonographic findings of the entheses revealed that while there is good correlation with the Achilles tendon and patellar tendon origin, it is not as good for other sites. Further research is necessary in this area (9).

- IPART sponsored a study designed to identify and characterize psoriasis and PsA patients in Ontario administrative data which provided algorithms to identify patients with psoriasis and PsA in Ontario Administrative Registries which was utilized for prevalence and incidence studies, delay in diagnosis and mortality in the Ontario population (10).

- Remission in PsA is not well defined. Most studies consider low disease activity as an appropriate outcome. We defined remission in PsA as having no tender or swollen joints, no inflammatory back pain, no tender entheseal sites, minimal skin involvement (BSA<1%) and patient reported outcomes as per the MDA criteria. We used imputation approach to determine remission status for visits with incomplete criteria for each patient. Among the 985 patients included in the study 18% achieved a remission at least once and 9% achieved sustained remission on at least 2 consecutive visits. Higher BMI reduced the chance while the use of biologics increased the chance of achieving remission (12).

- We revisited the question of malignancy in PsA now that many of our patients are receiving biologics agents. Our updated malignancy study used our databases of both PsA and PsC, with linkages with Cancer Care Ontario and the Death Registry to ascertain inclusion of all documented malignancies. We found that 11% of our cohort developed cancer. The overall risk of malignancy was not different from the rest of the population. However, skin cancer was the only specific cancer that had a higher incidence than the general population. There was insufficient evidence to suggest an increased risk of malignancy with biologics use (15).

- We participated in an international study to look at the phenotype of axial Spondyloarthritis (axSpA). We contributed 40 patient scenarios from our cohort. The study found that HLA-B27 positive axSpA patients had more severe radiographic damage, more marginal syndesmophytes that were more

frequently symmetrical compared to HLA-B27 negative patients, regardless of underlying diagnosis (16).

- A study of osteoporosis and bone mineral density (BMD) testing in our cohort revealed that 214 of 1074 patients had BMDs which demonstrated osteopenia in 45.4% and osteoporosis in 13%. The frequency of osteoporosis is similar to the general population. Increased age, menopause, and burden of disease were associated with a higher change of getting a BMD test. Increased BMI and biologic use were associated with a lower chance of having osteoporosis (17).

- Having demonstrated that patients with psoriatic disease have a higher incidence of cardiovascular events we further investigated the incidence of risk factors of heart failure. This study included 1994 patients with psoriatic disease. The incidence of first heart failure event was 2.85/1000 patient years. Independent predictors for heart failure events were ischemic heart disease, disease burden and physical function. Being in MDA was protective for heart failure events (18).

- We explored the use of cannabis among the psoriatic disease patients in the TWH IPART cohort and found that about a third of the patients were using cannabis. There did not appear to be a difference in pain reporting in cannabis users compared to non-users (Abs 2).

- We found that there is a delay in consultation in our cohort.

TRANSLATIONAL STUDIES

- Our previous studies suggested that the λ_1 for PsA was higher for PsA than psoriasis without arthritis (PsC). However, a recent analysis of heritability using mixed effect modelling methodology to determine the additive contribution of common single nucleotide polymorphisms (SNPs) from genome-wide association studies based on the IPART cohort demonstrated that while both PsA and PsC exhibit considerable heritability, there is a greater contribution from cutaneous psoriasis (3).

- We have previously published on the increased levels of the chemokine CXCL10 in patients with PsA compared to patients with PsC. We have now extended these observations to demonstrate that patients with PsC who go on to develop PsA have higher levels of CXCL10 initially, but that these levels drop after the development of PsA. This is a unique observation which does not happen in patients with PsC who do not develop PsA in whom the levels remain stable. These results suggest that CXCL10 may be a marker for the development of PsA among patients with psoriasis (11).

- A study of 32 patients who underwent 60 joint injections with information available at 3-6 months' post injection demonstrated that there was clinical response in 41.7%. Only treatment with biologics was significantly associated with response. There was no association between synovial fluid serine proteinas activity and response to intra-articular corticosteroid injection (13).

STUDIES PRESENTED AT MEETINGS IN 2020

- Since we had previously demonstrated a role for CXCL10 and its receptor CXCR3 in PsA, and both are vulnerable to inactivation through truncation by DPP4, we examined the role of dipeptidyl peptidase 4 (DPP4) in psoriatic disease. We demonstrated that DPP4 enzymatic activity as well as serum DPP4 and CXCL10 levels were higher in PsA than PsC. DPP4 enzymatic activity and serum levels negatively associated with serum CXCL10 in PsA patients. Serum CXCL10 levels decreased while DPP4 levels significantly increased following treatment. Both DPP4 and CXCL10 levels were significantly higher in

PsA synovial fluid compared to osteoarthritis synovial fluid. There was a strong correlation between matched serum and SF samples DPP4 and CXCL10 levels (Abs 1).

- We explored the use of cannabis among our psoriatic disease patients. Some 30% of the patients reported cannabis use within the previous year. Cannabis users were younger, had shorter PsA duration and had poorer mental health as measured by the SF-36. However, other measures of health related quality of life and functions were comparable between the two groups, which does not support the responders' perception that cannabis aided in sleep and arthritis pain relief (Abs 2).

- We sought to determine whether our patients received their consultation within the 6-weeks of referral window recommended by the CRA/SPARCC treatment recommendations. We found that only 25.6% of the patients referred between 2013 and 2019 were seen within the recommended time. The median wait time was 78.5 days. The most common reason for delay was lack of spots in the PsA clinic, suggesting that there is a need for more rheumatologists (Abst 3).

- An analysis of biologic therapy in our cohort revealed that the most common biologist used by our patients were etanercept and adalimumab. There were significant number of switches (Abst 4).

- A prediction tool for PsA was developed from our psoriatic disease cohort (Abst 5).

- We determined the prevalence and risk factors for musculoskeletal surgery among patients with PsA (Abst 6)

- The efficacy of anti-rheumatic drugs in the treatment of enthesitis was investigated and showed that there was no specific benefit for any particular type of DMARD (Abst 7).

- Targeted metabolomics and cardiac biomarker analysis in our cohort demonstrated that these are useful in identifying PsA patients with cardiovascular event (Abst 8,9)

- An integrative approach to identify heritable and de novo genomic variations in arthritis mutilans was used and identified. (Abst 10).

- We studied our patients with PsA who have had monoclonal gammopathy of unknown significance (MGUS) and demonstrated that very few went on to develop multiple myeloma (abstract 11).

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EDUCATION, TRAINING & ADVOCACY COMPONENTS

IPART will continue to collaborate with the **Psoriatic Arthritis Research Program (PsARP),** UHN-Toronto Western Hospital, likewise spearheaded by Drs. Dafna D. Gladman (Director) and Vinod Chandran (Co-Director), with the following initiatives:

- **PsA Patient Advisory Committee** - One of our mandates as a research program is to ensure that the knowledge learned from this research is made available to our patients, their families and other interested lay groups. This is achieved by way of newsletters and annual patient symposiums. A PsA patient advisory committee has been formed to help in reviewing educational materials and provide feedback and suggest for the format of symposiums and bring forth ideas for other formats of

disseminating information to patients. The Patient Advisory Committee has been very helpful in setting the programs for the patient forms.

- **Psoriatic Arthritis Patient Forum** – Annually, PsARP and IPART jointly conduct a PsA patient forum that highlights presentations about causes of the diseases, recent advances in treatment of psoriasis and PsA, comorbidities, etc. These educational forums also feature other important related topics like diet, physiotherapy, skin, stress reduction and patient advocacy. Because of the COVID-19 pandemic, our last patient form was virtual and was very successful. We have colleagues discuss the COVID-19 pandemic, as well as virtual patient care which was very helpful for the patients.

- **Fellows Training** – Training of fellows is an important activity in the program, increasing potential future recruitment of rheumatologists. These fellows contribute significantly into the program and stipends are paid for each annually solicited from various sources. These fellows take active roles in the execution of the various projects on-going in the IPART and PsARP programs. Several of these have resulted in the publications described above.

- **Studentship** – Through the PsARP and IPART programs, medical students likewise take part in projects and core activities as outlined above. The program normally accepts 4-6 students each year. Because of the COVID-19 pandemic, we have not been able to accept summer students on site but have been able to engage some students remotely, and several have had a productive summer investigating our patients. The results of their studies will likely be presented next year.

- **IPART Annual Scientific and Investigator Meetings** – The IPART core investigators, collaborating site investigators and its key coordinators meet annually as one of its medium of dissemination to its stakeholders, to coordinate research activities and unveil new discoveries. In 2020, we planned an in-person meeting in June 2020 but postponed it for December 2020; however, due to a provincial directive not allowing in-person gatherings and events, in addition to travel restrictions until now, we were unable to conduct a meeting in 2020 altogether.

  For **2021**, IPART decided to conduct a virtual ZOOM webinar format meeting instead, and this is taking place on March 19, 2021 from 1-4PM, eastern standard time. At which time, IPART's research updates and progress report will be unveiled.

- **Knowledge Transfer and Exchange** - Knowledge transfer occurs at several levels. One is presentations at professional meetings and publications. These have been described in the previous pages. Another aspect of knowledge translation is with other stakeholders, which include patients. As described above, we do have a patient advisory committee who help us with research grant submissions and we also share information with our patients through the patient forums. Since the availability of the virtual meetings, we may consider having an IPART-wide patient forum as well.

INFRASTRUCTURE

The **International Psoriasis and Arthritis Research Team (IPART)** is a highly successful, international consortium of rheumatologists and dermatologists across Canada and the United States with expertise in genomics, inflammation, immunology and epidemiology. IPART was formed in 2007 and spearheaded by Dr. Dafna D. Gladman, its Principal Investigator.

IPART has five core sites namely:

Toronto, Ontario, CANADA	**Dr. Dafna D. Gladman,** Division of Rheumatology, University of Toronto, Toronto Western Hospital **Dr. Cheryl F. Rosen**, Division of Dermatology, University of Toronto, Toronto Western Hospital **Dr. Vinod Chandran**, Division of Rheumatology, University of Toronto, Toronto Western Hospital
St. John's, Newfoundland,	**Dr. Proton Rahman** - Division of Rheumatology and Genetics, Memorial University of Newfoundland
Vancouver, British Columbia, CANADA	**Dr. Jan Dutz** - Divisions of Rheumatology and Dermatology, University of British Columbia, Vancouver
Ann Arbor, Michigan, USA	**Dr. James T. Elder** - Division of Dermatology, University of Michigan, Ann Arbor, Michigan
Rochester, New York, USA	**Dr. Christopher Ritchlin** - Division of Rheumatology, University of Rochester, New York

IPART has other active collaborating sites across Canada and internationally as follows:

1) London, Ontario (University of Western Ontario – **Dr. Sherry Rohekar and Dr. Tristan Boyd**)
2) Winnipeg, Manitoba (Winnipeg Clinic – **Dr. Snezana Barac and Dr. Richard Haydey**)
3) Toronto, Ontario (Women's College Hospital – **Dr. Lihi Eder and Dr. Jensen Yeung**)
4) Haifa, Israel (Carmel Medical Center – **Dr. Devy Zisman**)
5) Detroit, MI (Henry Ford Health System – **Dr. Qing-Sheng Mi and Dr. So Yeon Paek**)
6) India (Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS) – **Dr. Vikas Agarwal**)
7) Ottawa, Ontario (University of Ottawa – **Dr. Sibel Aydin**)
8) Vancouver, BC (ARTUS Health Center - **Dr. Jonathan Chan** joined our core site at the University of British Columbia – Dr. Jan Dutz)
9) Vellore, India – (Christian Medical College - **Dr. Ashish Matthew and Dr. Debashish Danda**)
10) Quebec City, Quebec (CHU de Quebec, Université Laval – **Drs. Karen Adam, Paul Fortin and Louise Bessett)**

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At present, IPART is funded by multi-industry support from **ABBVIE, AMGEN, UCB, PFIZER, and ELI LILLY** granted through the IPART Toronto core site at the University Health Network, Toronto Western Hospital.

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NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases	**National Institutes of Health (NIH), National Institutes of Arthritis and Musculoskeletal and Skin Diseases**